Diabetic diarrhoea: a study on gastrointestinal motility, pH levels and autonomic function

■ Dag A. Sangnes[1,2] ⓘ, Georg Dimcevski[2,3] ⓘ, Jakub Frey[1] & Eirik Søfteland[1,4] ⓘ

From the [1] Department of Medicine, Haukeland University Hospital, Bergen, Norway; [2] Department of Clinical Medicine, University of Bergen, Bergen, Norway; [3] National Centre for Ultrasound in Gastroenterology, Haukeland University Hospital, Bergen, Norway; and [4] Hormone Laboratory, Haukeland University Hospital, Bergen, Norway

Abstract. Sangnes DA, Dimcevski G, Frey J, Søfteland E. Diabetic diarrhoea: a study on gastrointestinal motility, pH levels and autonomic function. *J Intern Med.* 2021;**OO:**1-13. https://doi.org/10.1111/joim.13340

Background. Chronic diarrhoea is a common, but poorly investigated diabetes complication. Autonomic neuropathy is a leading pathophysiological theory founded on old, small studies. Studies of gastrointestinal motility and pH levels are lacking.

Objectives. Using new diagnostic methods, we aimed to find out if diabetic diarrhoea was associated with alterations in gastrointestinal motility, pH levels and autonomic function.

Methods. Fifty-seven patients (42 women, 46 type 1 diabetes) were prospectively included. Symptoms were evaluated with the gastrointestinal symptom rating scale, defining $\geq$ 4 points as cases with diarrhoea. Patients scoring < 4 were used as controls. We used the wireless motility capsule to measure gastrointestinal transit times, pH levels and contractility parameters. Autonomic function was assessed by measuring heart rate variability, baroreflex sensitivity and orthostatic hypotension.

Results. Seventeen patients (30%) had diarrhoea. Compared with controls, cases had slower gastric emptying (21:46 vs. 4:14, h:min, $p = 0.03$) and faster colonic transit (18:37 vs. 54:25, $p < 0.001$). Cases had increased intraluminal pH in the antrum (2.4 vs. 1.2, $p = 0.009$), caecum (7.3 vs. 6.4, $p = 0.008$) and entire colon (7.1 vs. 6.7, $p = 0.05$). They also had a decreased pH difference across the pylorus (3.3 vs. 4.9, $p = 0.004$) and ileocaecal junction (0.6 vs 1.0, $p = 0.009$). The groups did not differ in autonomic function, but diastolic blood pressure drop correlated $r_s = -0.34$ ($p = 0.04$) with colonic transit time.

Conclusions. Patients with diabetic diarrhoea had altered gastrointestinal transit and intraluminal pH levels, but minimal changes in autonomic function. Our results suggest that tests of gastrointestinal function are clinically useful in diabetic diarrhoea.

Keywords: autonomic dysfunction; diabetic diarrhoea; diabetic gastroenteropathy; gastrointestinal transit; intraluminal pH levels; wireless motility capsule

Abbreviation: GSRS, Gastrointestinal Symptom Rating Scale

Introduction

Chronic diarrhoea affects more than 10% of diabetes patients and often leads to impaired quality of life [1,2]. Evaluation can be challenging, as diabetes patients are at increased risk for developing other conditions leading to diarrhoea, like coeliac disease, pancreatic exocrine insufficiency and inflammatory bowel disease [3–7]. Diarrhoea may also come from dietary factors or common antidiabetic drugs like metformin and glucagon-like peptide-1 agonists [8–11]. However, in half of all patients, the diarrhoea will be attributed to alterations in intestinal motility and secretion secondary to diabetic gastroenteropathy [12]. Diabetic gastroenteropathy can affect any portion of the gastrointestinal tract, leading to manifestations like oesophageal dysmotility, gastroparesis and intestinal hyper- or hypomotility [11,13,14]. When these patients present with chronic diarrhoea, it has been termed diabetic diarrhoea [12]. Here, the diarrhoea is typically nonbloody and painless, with

a high-volume, watery consistence. It may be nocturnal and can lead to faecal incontinence [1,12].

Although being recognized for almost a century, little is known about the pathophysiological mechanisms behind diabetic diarrhoea [13]. The leading theory of autonomic neuropathy was established after finding high covariance between neuropathy and diarrhoea in case studies and a clinical resemblance with patients who had undergone vagotomy or sympathectomy [15,16]. Later studies are limited in numbers, inconclusive, and there are no studies using new technology for assessing autonomic function [13,15,17–19]. Studies investigating intestinal transit and contractility are also lacking. One explanation may be that these measurements previously have been laborious and patient unfriendly, limiting their availability to specialized centres. Recently, the wireless motility capsule has emerged as a promising method, simultaneously measuring transit times and contractility throughout the gastrointestinal tract whilst patients are ambulant [20]. The capsule also measures pH levels [21]. This is relevant since diarrhoeal disorders are associated with both intraluminal and systemic pH level alterations [22,23]. So far, these measurements are unexplored in diabetic diarrhoea, but there are noteworthy findings from studies on patients with irritable bowel syndrome and small intestinal bacterial overgrowth [24,25].

In this study, our main hypothesis was that diabetes patients with diarrhoea had altered gastrointestinal transit times. We also hypothesized that they had altered intraluminal pH levels, reduced contractility and autonomic dysfunction. To investigate this, we examined a cohort of diabetes patients with gastrointestinal symptoms and suspected gastroenteropathy using wireless motility capsule and autonomic function tests.

Methods

Study population

Between 2014 and 2018, we prospectively included diabetes patients with symptoms suggestive of gastroenteropathy into a cross-sectional, observational study. All patients had been referred for diagnostic evaluation at a tertiary centre at Haukeland University Hospital, Bergen, Norway. Inclusion criteria were type 1 or type 2 diabetes, age over 18 years and normal upper endoscopy. Exclusion criteria were pregnancy, breastfeeding,

active malignancy (defined as any cancer not in complete remission for the last six months) and lack of ability to comply with the study protocol.

Patients were admitted to the hospital during the study, where they were interviewed and examined by a physician, and delivered blood, urinary and faecal samples (Table 1). They were kept on intravenous glucose-insulin infusion during fasting and examinations, with a target glucose level between 4 and 10 mmol/L.

Wireless motility capsule

The wireless motility capsule (SmartPill; Medtronic, Minneapolis, USA) is a 26×13 mm indigestible, single-use capsule. It registers temperature (range 25–49°C), pH (0.5–9.0) and pressure (0–350 mmHg) throughout the gastrointestinal tract. During the test, data are transferred to a portable data receiver and afterwards downloaded to a computer. For analysis, we used MotiliGI® software version 3.0 (Medtronic).

We used stereotypical pH profiles to define transit times [21]: Gastric emptying time (capsule ingestion – pylorus), small bowel transit time (pylorus – ileocaecal junction), colonic transit time (ileocaecal junction – capsule expulsion); and whole gut transit time (capsule ingestion – capsule expulsion). Antral pH was defined as median pH for the last 15 min before the pylorus; duodenal pH the first 15 min after the pylorus; ileum the last 15 min before the ileocaecal junction; caecum the first 15 min after the ileocaecal junction; and rectum the last 15 min before capsule expulsion. Delta pylorus was defined as the difference between duodenal and antral pH; delta ileocaecal junction the difference between ileal and caecal pH.

We also measured the motility index and contractions per minute in the whole stomach, small bowel and colon [20]. To determine the ileocaecal junction pressure, we used the method proposed by Chander Roland et al., identifying the maximum pressure for the last 4 min prior to the ileocaecal junction pH drop [25].

All patients had to pause medications potentially altering intestinal function before and during the study. We have specified details in a previous article, together with a description of the test meal and initiation protocol [26]. Patients continued other regular medications, provided doses had been

TABLE 1. *Clinical characteristics of all diabetes patients and a comparison between patients with diarrhoea and controls*

Variables	All patients (n = 57)	Comparison of groups		p value	Effect size
		Controls (n = 40)	Cases (n = 17)		
General demographics					
Women, n	42 (74%)	30 (75%)	12 (71%)	0.73	0.05
On disability benefits, n	36 (64%)	25 (63%)	11 (69%)	0.66	0.06
Age, years	50 (39–56)	50 (40–56)	51 (31–57)	0.57	0.08
BMI, kg/m²	25.7 (22.1–29.6)	26.5 (22.1–30.4)	24.8 (21.5–28.2)	0.41	0.11
Smoking (never/previous/current), n	18/22/17	16/13/11	2/9/6	0.10	0.28
Alcohol (0/<1/1–7/≥7 units/week), n	20/18/15/3	12/12/13/2	8/6/2/1	0.39	0.23
Diabetes status					
Type 1 diabetes, n	46 (81%)	32 (80%)	14 (82%)	0.84	0.03
Diabetes duration, years	26 (16–37)	28 (19–39)	23 (13–31)	0.10	0.22
Late complications (0/1/≥2), n	17/13/27	13/9/18	4/4/9	0.78	0.09
Retinopathy, n (%)	32 (56%)	23 (58%)	9 (53%)	0.75	0.04
Nephropathy, n (%)	15 (26%)	10 (25%)	5 (29%)	0.73	0.05
Polyneuropathy, n (%)	25 (44%)	16 (40%)	9 (53%)	0.37	0.12
Diabetic wounds, n (%)	7 (12%)	4 (10%)	3 (18%)	0.42	0.11
Cardiovascular disease, n (%)	5 (9%)	2 (5%)	3 (18%)	0.12	0.21
Any other complication, n (%)	9 (16%)	6 (15%)	3 (18%)	0.80	0.03
Biochemistry					
B-HbA1c, %/mmol/mol	8.1 (7.2–9.1) / 65 (55–76)	8.1 (7.3–8.9) / 65 (56–74)	8.0 (7.2–10.7) / 64 (55–93)	0.64	0.06
P-Glucose at test start, mmol/L	9.0 (6.6–11.3)	8.9 (6.8–11.2)	9.0 (5.6–12.4)	0.92	0.01
S-TSH, mIE/L	1.4 (0.8–2.0)	1.6 (0.9–2.0)	1.4 (0.8–2.1)	0.85	0.03
P-fT4, pmol/L	15.8 (14.5–18.9)	16.3 (14.9–19.4)	14.7 (13.6–17.8)	0.050	0.27
U-ACR, mg/mmol	1.6 (0.6–5.2)	1.0 (0.5–3.6)	3.5 (0.8–7.3)	0.09	0.24
F-Calprotectin, mg/kg	16 (15–42)	15 (15–39)	18 (15–43)	0.70	0.06
F-Elastase-1, mg/g	487 (283–500)	445 (283–500)	500 (322–500)	0.12	0.23

Results are presented as median (quartiles) unless otherwise indicated. Frequencies are given as n (%), where percentages are calculated from the total n in each column. Cases are defined by GSRS diarrhoea score ≥4 points; controls <4. Biochemical reference values as used at Haukeland University Hospital (presented on https://analyseoversikten.no): B-HbA1c, 4.0%–6.0%/20–42 mmol/mol; P-Glucose 4.0–6.0 mmol/L; S-TSH, 0.40–4.50 mIE/L; P-fT4, 8.0–21.0 pmol/L; U-ACR, 0 -2.5 mg/mmol; F-Calprotectin, <50 mg/kg; and F-Elastase-1, <200 mg/g.
Abbreviations: ACR, Albumin to creatinine ratio; B-, Whole blood; F-, Faecal; FT4, Free thyroxine; GSRS = Gastrointestinal Symptom Rating Scale; P-, Plasma; S, Serum; TSH, Thyroid stimulating hormone; U-, Urinary.

stable for 3 months. Intake of alcohol was prohibited, and patients were asked to refrain from smoking and strenuous physical activity.

Autonomic function tests

We assessed heart rate variability at rest and baroreflex sensitivity using the Heart Rhythm Scanner PE and the Biocom 5000 Bluetooth ECG Recorder (Biocom Technologies, Poulsbo, USA). We have described the heart rate variability protocol in a previous paper [27]. To measure baroreflex sensitivity, patients took deep breaths at a rate of five per minute. Thereafter, actual values were compared with predicted normative age-adjusted values by the software. Finally, we assessed orthostatic hypotension using Welch Allyn ProBP 3400 (Welch Allyn Inc., Skaneateles Falls, USA) following a standardized protocol measuring supine, resting blood pressure and standing blood pressure after 1 and 3 min. Orthostatic hypotension was defined as a drop in systolic blood pressure of ≥ 20 mm Hg or diastolic blood pressure ≥ 10 mm Hg from supine to standing position [28].

Symptom assessments

Symptoms were evaluated by physician interview and using the Gastrointestinal Symptom Rating Scale (GSRS), a questionnaire validated for assessing the occurrence and severity of upper and lower gastrointestinal symptoms during the last week [29]. GSRS includes 15 questions, each rated from no discomfort (zero points) to very severe discomfort (six points). Diarrhoea syndrome (hereafter named 'diarrhoea') is derived by taking the mean of the individual symptoms: increased passage of stools, loose stools and urgent need for defecation [29]. We used a cut-off value of ≥ 4 points, corresponding to the 75th percentile, to define cases with diarrhoea. Those scoring <4 were used as controls. We also looked at correlations between diarrhoea score and each wireless motility capsule and autonomic function test parameter.

Statistical analysis

Continuous variables are stated as median (quartiles) and categorical variables as n (%). We used the Mann–Whitney U test to compare two continuous variables, using r as an effect size estimate ($r = z/$square root of the total number of cases, N). To examine associations between continuous variables, we used Spearman's Rank Order Correlation test (r_s) with bootstrapped 95% confidence inter-

vals (CI) and the coefficient of determination ($R^2 = r_s$ squared). We used Pearson's chi-square test to compare categorical variables with Cramér's V (ϕ_c) as an effect size estimate. Agreement was evaluated using Cohen's kappa measure of agreement (κ). Statistical significance was defined as $p \leq 0.05$. Analyses were performed using IBM SPSS Statistics (Version 27, IBM Corporation, USA), except effect size estimates for the Mann–Whitney U test and R^2, which were calculated using Microsoft Excel (Version 2102, Microsoft Corporation, USA). For both r and ϕ_c, effect sizes can be interpreted using Cohen's criteria (1988): Small effect (>0.10), medium effect (>0.30) and large effect (>0.50) [30].

Ethical considerations

All participants submitted oral and written consent prior to study-related procedures. The study was approved by The Western Norway Regional Medical Ethics Committee (2015/58) and conducted in accordance with the Declaration of Helsinki.

Results

Seventy-two patients were included in the study, of which 68 were examined with wireless motility capsule. We were unable to identify the ileocaecal junction in three patients, precluding determination of small bowel and colonic transit. Of the remaining 65 patients, eight had missing GSRS data, leaving 57 available for comparisons. An inclusion flowchart is shown in Fig. 1.

Clinical characteristics

Clinical characteristics are presented in Table 1. Fifty patients (88%) used insulin, three (5%) sodium-glucose cotransporter-2 inhibitors, two (4%) glucagon-like peptide-1 agonists, two (4%) dipeptidyl peptidase-4 inhibitors and one (2%) used pioglitazone. Four patients (7%) used antidiarrhoeal medications. A detailed list of medications are provided in Table S1.

We identified 17 (30%) cases with a diarrhoea score ≥ 4 points, compared to 12 (21%) reporting diarrhoea during physician interview, $\kappa = 0.68$, $p < 0.001$. Median score in all patients were 2.7 (0.5–4.0), with no difference between women (2.3, 0.6–4.0) and men (2.7, 0–5.0, $p = 0.81$, $r = 0.03$), nor between type 1 diabetes (2.8, 0.7–4.1) and type 2 diabetes (2.0, 0–4.0, $p = 0.46$, $r = 0.10$). Those with one or more late diabetes complications scored 3.0 (0.8–4.3), those without 0.7 (0–3.5), $p = 0.06$,
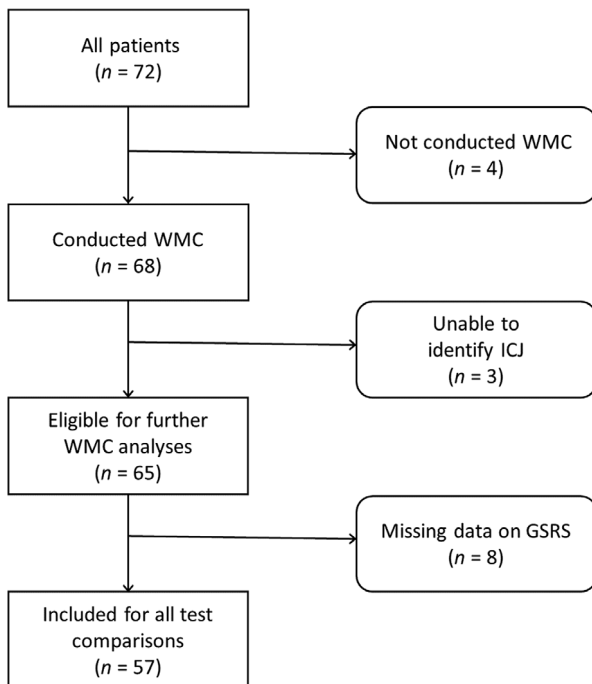
FIGURE 1 Inclusion flow chart.

$r = 0.25$. Cases and controls did not differ in age, BMI, diabetes duration, HbA1c, faecal elastase-1, nor faecal calprotectin levels.

Transit times, pH levels and contractility parameters

A comparison of transit times, pH levels and contractility parameters between cases and controls are presented in Table 2. Transit times are also displayed in Fig. 2, pH levels in Fig. 3. Correlations between all wireless motility capsule measurements and the continuous GSRS diarrhoea score are shown in Table S2.

We found that cases had slower gastric emptying ($p = 0.03$) and faster colonic transit ($p < 0.001$) than controls. We found no difference in small bowel transit ($p = 0.11$) nor whole gut transit ($p = 0.16$). Colonic transit correlated with the diarrhoea score, $p = 0.006$.

We found that cases had increased antral pH ($p = 0.009$) and decreased pH difference across the pylorus ($p = 0.004$). Cases also had increased colonic pH ($p = 0.05$), increased caecal pH ($p = 0.008$) and decreased pH difference across the ileocaecal junction ($p = 0.009$). Antral pH ($p = 0.02$), ileal pH ($p = 0.03$), caecal pH ($p = 0.006$) and pH differences across the pylorus ($p = 0.001$) and ileocaecal junction ($p = 0.04$) all correlated with diarrhoea scores.

We found no correlations between transit times and pH in the stomach ($r_s = 0.02$, 95% CI -0.24–0.28, $R^2 = 0.0\%$, $p = 0.86$), small bowel ($r_s = 0.10$, 95% CI -0.16–0.34, $R^2 = 1.0\%$, $p = 0.46$), nor colon ($r_s = -0.14$, 95% CI -0.37–0.12, $R^2 = 2.0\%$, $p = 0.32$). There was no correlation between pH difference across the ileocaecal junction and colonic transit time, $r_s = 0.13$, 95% CI -0.12–0.38, $R^2 = 1.7\%$, $p = 0.34$.

We found no difference between cases and controls in any of the contractility parameters, all $p > 0.23$. Neither did we identify any significant correlations with the GSRS diarrhoea score, all $p > 0.35$.

Autonomic function tests

In Table 3, we present a comparison of autonomic function tests between cases and controls, as defined by the GSRS cut-off value. Correlations between autonomic function test parameters and the GSRS diarrhoea score are shown in Table S3. In cases, we found a trend towards increased diastolic blood pressure drop at 3 min, $p = 0.054$. We found no difference in any of the other parameters (all $p > 0.10$) and no significant correlations (all $p > 0.10$). Thirteen controls (33%) and eight cases (57%) had orthostatic hypotension, $\chi^2 (1) = 2.65$, $p = 0.10$, $\phi_c = 0.22$. Of all autonomic function test parameters, only diastolic blood pressure drop at 0 min correlated significantly ($p = 0.04$) with colonic transit time, Table S4.

Discussion

In this study we aimed to investigate the association between diabetic diarrhoea, intestinal motility, pH levels and autonomic dysfunction. By examining diabetes patients with wireless motility capsule, we found that patients with diarrhoea had slower gastric emptying and faster colonic transit than controls. They also had an increased pH level in the stomach's antrum, caecum and entire colon and decreased pH difference across the pylorus and ileocaecal junction. We found a moderate negative correlation between diastolic blood pressure drop and colonic transit time, but no other associations between diabetic diarrhoea and autonomic dysfunction.

TABLE 2. *Wireless motility capsule measurements of transit times, pH levels and contractility parameters: a comparison of diabetes patients with diarrhoea and controls*

| Variables/location, unit	Controls	Cases	*p* value	Effect size
Transit times				
Stomach, h:min	4:14 (3:11–19:26)	21:46 (3:58–47:12)	0.03	0.29
Small bowel, h:min	4:44 (3:51–6:03)	3:36 (2:24–6:52)	0.11	0.21
Colon, h:min	54:25 (22:56–78:11)	18:37 (7:23–35:08)	<0.001	0.49
Whole gut, h:min	72:44 (38:11–105:32)	57:05 (31:59–74:07)	0.16	0.19
pH levels				
Stomach (whole)	1.6 (1.1–2.8)	1.6 (1.4–3.6)	0.45	0.10
Antrum	1.2 (0.8–1.8)	2.4 (1.5–2.9)	0.009	0.35
Delta pylorus	4.9 (3.6–5.4)	3.3 (2.3–4.4)	0.004	0.38
Small bowel (whole)	7.4 (7.0–7.6)	7.1 (6.6–7.7)	0.35	0.12
Duodenum	6.2 (5.6–6.6)	5.9 (4.8–6.5)	0.25	0.15
Ileum	7.7 (7.3–7.8)	7.8 (7.4–8.4)	0.19	0.17
Delta ICJ	1.0 (0.7–1.5)	0.6 (0.3–0.9)	0.009	0.35
Colon (whole)	6.7 (6.2–7.0)	7.1 (6.7–7.3)	0.05	0.26
Caecum	6.4 (5.9–6.9)	7.3 (6.7–7.7)	0.008	0.35
Rectum	7.5 (7.0–7.9)	7.4 (6.4–7.8)	0.23	0.16
Contractility parameters				
Gastric MI, mmHg·s/min	40.2 (27.0–65.2)	42.6 (32.8–75.0)	0.61	0.07
Gastric Ct, number/min	1.1 (0.8–1.7)	1.2 (0.8–2.0)	0.58	0.07
Small bowel MI, mmHg·s/min	136.0 (84.5–226.1)	182.7 (106.4–266.6)	0.23	0.16
Small bowel Ct, number/min	3.9 (2.3–5.2)	4.1 (2.8–6.3)	0.38	0.12
ICJ pressure, mmHg·s/min	40.6 (25.1–62.9)	39.0 (23.9–75.8)	0.62	0.07
Colonic MI, mmHg·s/min	148.6 (104.8–254.3)	132.7 (88.5–259.8)	0.77	0.04
Colonic Ct, number/min	1.3 (1.1–2.0)	1.7 (1.0–2.7)	0.50	0.09

Results are presented as median (quartiles). Cases are defined by GSRS diarrhoea score ≥4 points; controls <4. Transit times, pH variables and contractility parameters are defined in the Methods section.

Abbreviations: Ct, Contractions; GSRS, Gastrointestinal Symptom Rating Scale; ICJ, Ileocaecal junction; MI, Motility index.

TRANSIT TIMES
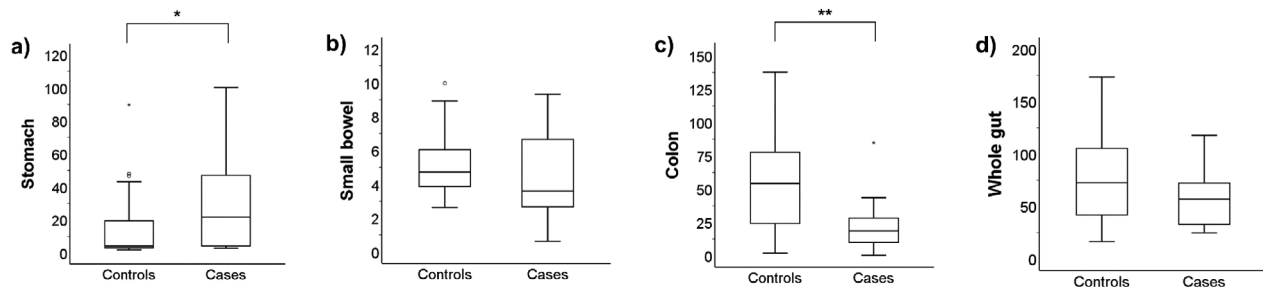
FIGURE 2 Box-plots showing regional transit times in controls and cases. Statistical significance of p ≤ 0.05 are marked by *; p < 0.01 are marked by **. Results are given as median (quartiles). Transit times (hours: minutes): (a) Stomach: 4:14 (3:11–19:26) in controls versus 21:46 (3:58-47:12) in cases, p = 0.03; (b) Small bowel: 4:44 (3:51–6:03) versus 3:36 (2:24-6:52), p = 0.11; (c) Colon: 54:25 (22:56–78:11) versus 18:37 (7:23–35:08), p < 0.001; Whole gut: 72:44 (38:11–105:32) versus 57:05 (31:59–74:07), p = 0.16.

pH VALUES
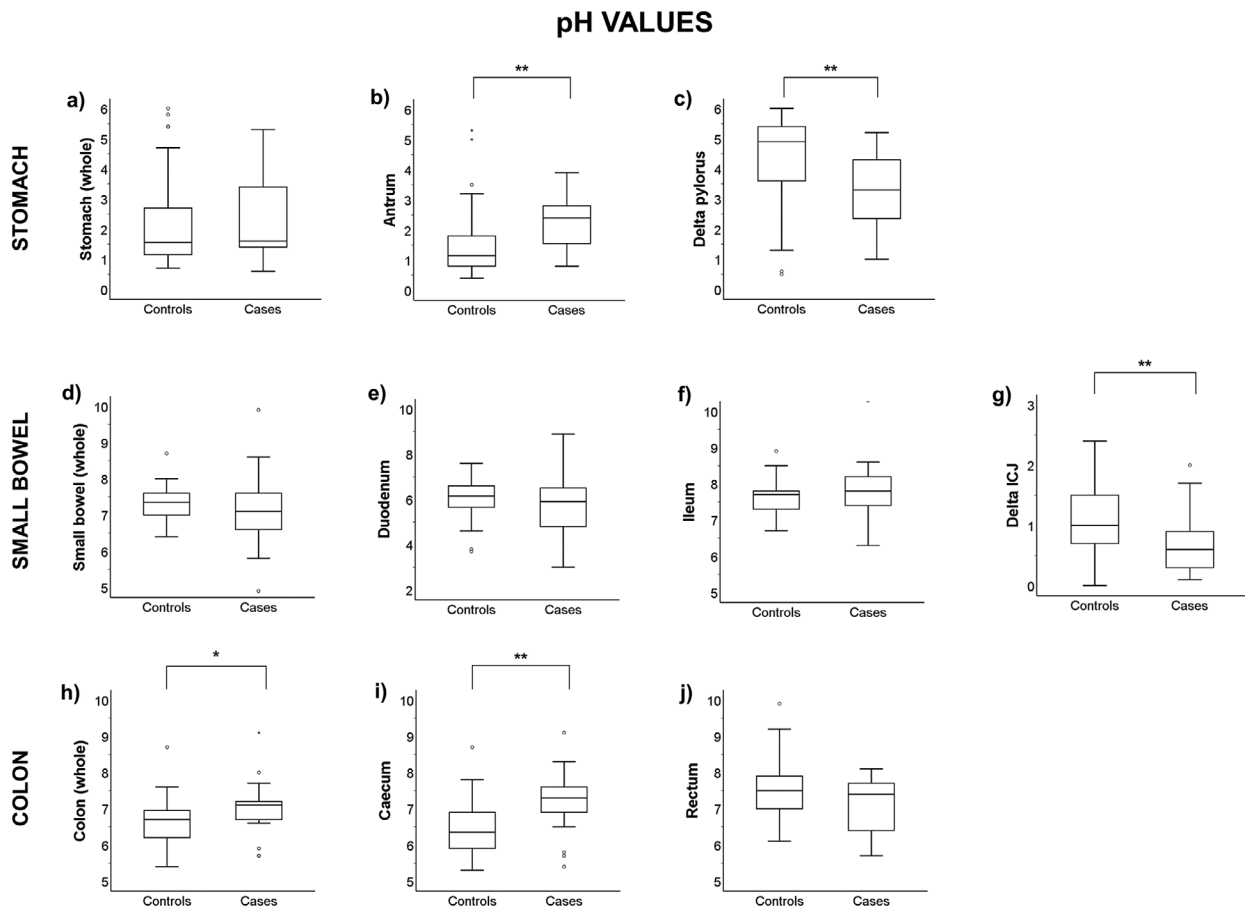
FIGURE 3 *Box-plots showing regional pH levels in controls and cases. Statistical significance of $p \leq 0.05$ are marked by *; $p < 0.01$ are marked by **. Results are given as median (quartiles). Stomach pH levels: (a) Stomach (whole): 1.6 (1.1–2.8) in controls versus 1.6 (1.4–3.6) in cases, $p = 0.45$; (b) Antrum: 1.2 (0.8–1.8) versus 2.4 (1.5–2.9), $p = 0.009$; (c) Delta pylorus: 4.9 (3.6–5.4) versus 3.3 (2.3–4.4), $p = 0.004$. Small bowel pH levels: (d) Small bowel (whole): 7.4 (7.0–7.6) versus 7.1 (6.6–7.7), $p = 0.35$; (e) Duodenum: 6.2 (5.6–6.6) versus 5.9 (4.8–6.5), $p = 0.25$; (f) Ileum: 7.7 (7.3–7.8) versus 7.8 (7.4–8.4), $p = 0.19$; (g) Delta ICJ: 1.0 (0.7–1.5) versus 0.6 (0.3–0.9), $p = 0.009$. Colonic pH levels: (h) Colon (whole): 6.7 (6.2–7.0) versus 7.1 (6.7–7.3), $p = 0.05$; (i) Caecum 6.4 (5.9–6.9) versus 7.3 (6.7–7.7), $p = 0.008$; (j) Rectum 7.5 (7.0–7.9) versus 7.4 (6.4–7.8), $p = 0.23$. Abbreviation: ICJ = Ileocaecal junction.*

Previous studies of intestinal dysmotility in diabetic diarrhoea have shown divergent results [31–36]. Some have found an association between diabetic diarrhoea, prolonged transit time and small intestinal bacterial overgrowth [31,33,34]. Others have found results similar to ours, with shortened intestinal transit, some also identifying a correlation with autonomic dysfunction [12,32,35,36]. Theoretically, autonomic dysfunction may induce intestinal dysmotility through several pathways. Loss of inhibitory input through damaged sympathetic innervation could explain the rapid transit seen in our diarrhoea patients [17]. Stimulation of alpha-adrenergic receptors on enterocytes

is also important for intestinal fluid absorption, and autonomic dysfunction could lead to increased colonic fluid levels and watery diarrhoea [1,13]. Alterations in the sympathetic and parasympathetic nervous systems have been found in several human pathological studies [17,37]. Despite this, Whalen and colleagues demonstrated intact efferent autonomic function in patients with diabetic diarrhoea when investigating intestinal motility in response to intravenous stimulation by adrenergic and cholinergic agents [38]. They did, however, find reduced pain response to intrajejunal balloon distention, indicating afferent dysfunction [38]. Similar findings have been made in the oesophagus,

TABLE 3. *Autonomic function tests: a comparison of diabetes patients with diarrhoea and controls*

Variable, unit	Controls	Cases	*p* value	Effect size
Heart rate variability (time-domain measures)				
Mean heart rate, bpm	74.1 (66.8–86.3)	71.3 (64.2–84.4)	0.63	0.07
Mean NN	802.8 (689.9–939.6)	841.4 (745.7–948.5)	0.51	0.11
SDNN, ms	24.6 (12.7–35.0)	20.1 (15.0–30.7)	0.70	0.06
RMSSD, ms	15.8 (6.9–26.9)	14.0 (11.7–21.1)	0.64	0.07
Heart rate variability (frequency-domain measures)				
Total power, ms^2	67.8 (21.2–272.8)	80.0 (5.1–219.1)	0.59	0.08
Very low frequency, ms^2	54.1 (19.5–132.3)	60.6 (13.8–129.1)	1.00	0.00
Low frequency, ms^2	26.5 (4.9–54.7)	30.0 (4.3–68.5)	0.84	0.03
High frequency, ms^2	10.6 (4.1–48.8)	14.3 (3.4–34.2)	0.92	0.02
LF norm, nu	58.6 (39.1–78.6)	62.8 (45.1–74.2)	0.69	0.06
HF norm, nu	41.4 (21.4–61.0)	37.2 (25.9–54.9)	0.69	0.06
LF/HF ratio	1.4 (0.7–3.7)	1.7 (0.8–3.0)	0.66	0.07
Baroreflex sensitivity				
Standard deviation of HR	3.3 (2.2–5.1)	4.2 (2.2–4.4)	0.92	0.02
Maximal variance of HR	11.0 (5.2–16.0)	6.9 (5.0–11.3)	0.28	0.16
Mean variance of HR	6.8 (3.0–11.5)	4.8 (3.2–8.1)	0.52	0.09
E/I ratio	1.09 (1.03–1.18)	1.07 (1.04–1.14)	0.74	0.05
Orthostatic tests				
30:15 ratio	1.06 (1.03–1.19)	1.06 (1.03–1.11)	0.47	0.11
Resting systolic BP	122 (112–134)	126 (115–138)	0.16	0.19
Resting diastolic BP	75 (66–82)	77 (65–84)	0.64	0.06
Systolic BP drop at 0 min	3 (-3–15)	25 (-1–31)	0.32	0.17
Diastolic BP drop at 0 min	3 (-4–8)	10 (2–16)	0.10	0.27
Systolic BP drop at 1 min	2 (-4–18)	3 (-8–21)	0.97	0.01
Diastolic BP drop at 1 min	1 (-6–6)	2 (-6–11)	0.55	0.08
Systolic BP drop at 3 min	2 (-4–12)	9 (1–27)	0.10	0.22
Diastolic BP drop at 3 min	-1 (-7–6)	4 (-1–18)	0.054	0.26

Results are presented as median (quartiles). Cases are defined by GSRS diarrhoea score ≥4 points; controls <4.
Abbreviations: BP, Blood Pressure; Bpm, Beats per minute; E/I ratio, Expiration/Inspiration ratio; GSRS, Gastrointestinal Symptom Rating Scale; HF norm, nu, High frequency normalized units; HR, Heart Rate; LF/HF ratio, low-frequency/high-frequency ratio; LF norm, nu, Low frequency normalized units; RMSSD, Root mean square of successive RR interval differences; SDNN, Standard deviation of NN intervals (inter-beat intervals where artefacts are removed).

duodenum and rectum, whilst gastric barostat studies have found the opposite in diabetic gastroparesis: visceral hypersensitivity [39–41]. Studies utilizing cardiac autonomic function tests in patients with diabetic gastroenteropathy, have also provided conflicting results [36,42,43].

In this study, we were unable to find any differences between cases and controls in heart rate variability or baroreflex sensitivity. Neither did we find any correlations between these parameters and diarrhoea score. We did, however, find a trend towards an increased orthostatic blood pressure drop in cases. In addition, we found a moder-

ate negative correlation with colonic transit time. These results could indicate a possible impairment of the sympathetic nervous system, although in such case, we would have expected to find differences in the high frequency spectres of the heart rate variability as well [28,44]. Overall, our results imply that other mechanisms than autonomic dysfunction are more prominent in the pathophysiology of diabetic diarrhoea. One explanation for our findings, could be that some patients in the comparator group also had enteric dysmotility. All patients had gastrointestinal symptoms and a clinical suspicion of gastroenteropathy, but controls differed with respect to not reporting diarrhoea. To

investigate this further, we found that a small proportion of controls had slow-transit constipation, as defined by GSRS and prolonged colonic transit [21,29]. However, excluding these patients did not alter the statistical significance of our original results.

Another pathophysiological theory potentially explaining our findings, is the loss of enteric neurons [17]. Through the production of nitrogen monoxide, these neurons have an important inhibitory effect on gastrointestinal peristalsis, and their depletion may lead to accelerated transit [1]. Apoptosis of enteric glial cells may aggravate neuronal loss [1]. Another possible mechanism may be reduced synthesis of sodium hydrosulphide, which acts as an inhibitor of intestinal smooth muscles [45]. There are conflicting results regarding the role of bile acid malabsorption in diabetic diarrhoea, but the theory has recently gained new impetus [12,46]. Increased levels of colonic bile acids might explain diarrhoea through several mechanisms, including a direct stimulatory effect on motility [47]. Small intestinal carbohydrate malabsorption may accelerate colonic transit through an increased fluid load, but short-chain fatty acids produced by fermentation of carbohydrates, slow down transit [48]. Additional mechanisms possibly contributing to dysmotility are neuroendocrine dysregulation, alterations of smooth muscle cells and loss of interstitial cells of Cajal [17]. Interestingly, the effect of hyperglycaemia is somewhat paradoxical: whilst chronic hyperglycaemia is central in the development of enteric neuropathy, and hence leads to accelerated transit, acute hyperglycaemia leads to delayed transit throughout the entire gastrointestinal tract [13,14,17].

Our study is the first to report intestinal pH alterations in patients with diabetic diarrhoea. Previously, this has been investigated in asymptomatic type 1 diabetes patients with peripheral neuropathy, finding decreased colonic pH levels and an increased pH difference across the ileocaecal junction compared to healthy controls [49,50]. Similar findings have been demonstrated in irritable bowel syndrome [24]. Normally, the pH level decreases more than one unit across the ileocaecal junction as a consequence of the more acidic environment in the caecum compared to the ileum [21]. This is mostly due to bacterial fermentation and production of short-chain fatty acids [49]. The magnitude of the ileocaecal pH drop has therefore been suggested as a proxy for the degree of fermentation in the proximal colon [51]. This may be increased in carbohydrate malabsorption or with heightened intake of fibre or other nonabsorbable sugars, the latter being a common cause of diarrhoea in diabetes [8,11,48]. When our cases had a decreased ileocaecal pH drop and an increased intracolonic pH profile than controls, this may reflect another microbial profile [21,49]. A number of factors may influence microbial composition, including diet, stool consistency, intestinal transit times and bile acids [52,53]. Theoretically, bile acid malabsorption may lead to colonic pH alterations directly, but this is so far not reported in studies. Different types of nutrients can influence pH levels indirectly, where increased production of ammonium in high protein-diets may lead to an alkaline intracolonic milieu [52]. In contrast to fermentation of carbohydrates, protein fermentation is most pronounced in lower parts of the colon, thus being a less likely cause of our caecal pH findings [53]. The interrelationship between intestinal transit and pH levels may be unpredictable: when colonic transit is rapid, pH levels may increase as bacteria have less time to ferment carbohydrates. At the same time, rapid transit may induce a shift towards lactate production, potentially lowering pH levels [52]. In this study, we found no association between pH levels and transit times.

Another possible explanation for our findings of a more alkaline caecal micromilieu may be altered activation of receptors facilitating bicarbonate secretion [54]. Interestingly, a study administering linaclotide to patients with irritable bowel syndrome with constipation, increased caecal pH, reduced colonic transit time and improved symptoms [51]. Linaclotide exerts its effect through increased luminal secretion of chloride and bicarbonate, in next case leading to increased efflux of water [51]. Ileocaecal valve dysfunction could lead to a decreased pH drop across the ileocaecal junction, as shown in patients with Crohn's disease who had undergone ileocaecal resection. Compared to controls, patients had increased pH in the caecum, whilst ileal pH levels were similar [55]. Ileocaecal valve dysfunction has also been associated with bacterial overgrowth [25]. However, we did not find any differences in ileocaecal junction pressure between cases and controls. Neither did we find any other differences in contractility parameters, but this should be explored in more detail in future studies. New studies are also needed to investigate the many potential causes of pH level alterations in diabetic diarrhoea,

including characterization of the microbiome and tests for bile acid malabsorption and bacterial overgrowth.

Previous studies have shown that wireless motility capsule examinations have large therapeutic consequences, providing new diagnoses in 50% of patients and changing treatment in 75% [56]. Our results also suggest that tests of gastrointestinal motility and pH levels have a role in the evaluation of diabetic diarrhoea, potentially guiding medical treatment. As an example, the patient with slow small bowel transit secondary to bacterial overgrowth, needs a different therapeutic approach than the patient with rapid colonic transit caused by enteric neuropathy. Many diabetes patients also have concurrent dysmotility in more than one gastrointestinal segment, evidenced by our diarrhoea patients having both delayed gastric emptying and rapid colonic transit [12,35,56]. Here, motility testing may help to tailorize pharmacological treatment [13,35,57,58]. Furthermore, alterations in pH levels or changes in luminal water content may affect intestinal drug delivery and absorption, being especially relevant for the release of active substances from drugs with controlled release formulations [14]. Although not yet investigated in diabetes, intestinal pH level alterations may also be linked to visceral sensitivity [59]. Finally, and crucially, the attention to this underreported and undertreated diabetes complication should be increased in health care providers. It is worrying that 30% of our study patients had diarrhoea, but only 7% used antidiarrhoeal medications.

There are some methodological considerations regarding our study. We used a validated questionnaire to assess bowel function [29]. As there are no predefined dichotomous cut-off values for the GSRS diarrhoea syndrome, we chose to define ≥4 points as cases with diarrhoea. This cut-off value was intentionally conservative, to maximize sensitivity for detecting true diarrhoea cases. A post hoc Kappa analysis, demonstrated a substantial agreement between our chosen cut-off for diarrhoea and clinical information gathered from physician interviews. Additionally, we performed correlation analyses showing similar results, thus strengthening our findings. Furthermore, exact localization of the wireless motility capsule is only possible when it passes the pylorus, ileocaecal junction or is expelled from the body [60]. The definition of gastrointestinal subsegments is therefore based on

temporal measurements in relation to these physiological landmarks. We utilized pH measurements 15 min before and after the pylorus and ileocaecal junction to determine pH in the adjacent subsegments, similar to the reference study by Wang and colleagues [21]. Other studies have used 30-min measurements or split the intestines into quartiles [49,50,61]. Compared to these approaches, 15-min measurements are preferential in patients with rapid transit. Due to the large variance in transit times, it also has an advantage over the quartile approach when it comes to interindividual comparisons. As stabilized pH values for >10 min is a criterion for manually determining the physiological landmarks, and the capsule has a negligible lag phase for detecting pH changes, 15-min measurements are likely sufficient [60]. Nevertheless, we support further validation studies to establish a consensus. Lastly, to investigate the association between diabetic diarrhoea and autonomic dysfunction, we measured heart rate variability, baroreflex sensitivity and orthostatic hypotension [28]. These are validated methods for assessing cardiac autonomic function and often used as a proxy for visceral autonomic neuropathy due to the lack of ideal tests for evaluating gastrointestinal autonomic function [27,62]. We have previously demonstrated an association between impaired rectal sensitivity, indicating autonomic neuropathy, and reduced cardiac autonomic function [40]. Others have also found an association between cardiac autonomic neuropathy and gastric vagal neuropathy [63].

Our study had some limitations. Being an exploratory study, we did not perform an a priori power analysis, but our main findings still had moderate effect sizes. However, our study may have been underpowered to identify a minor difference in small bowel transit. We also included patients having comorbidities or using drugs associated with diarrhoea (Table S1). Due to their frequency, excluding these patients would potentially introduce a selection bias. To assess eventual influence from comorbidities, we compared GSRS scores, only finding a marginally lower free thyroxine in diarrhoea patients (Table S1). Since the difference between groups was within the biological variation of free thyroxine, and both groups were in an euthyroid state, we find this unlikely to have had an influence on symptoms [64]. As for medications, we found higher diarrhoea scores in patients using opioids and antiepileptic drugs, both drug classes common in the treatment of painful neuropathy.

Considering this, we find it unlikely that our main findings could be explained by medications.

The main strength of our study was the use of state-of-the-art technology to assess gastrointestinal motility, pH levels and autonomic function. To our knowledge, this is the largest experimental study to date investigating diabetic diarrhoea. Whilst similar studies often have a retrospective design, we used prospective inclusion. Thereby we limited potential biases and were able to standardize patient characterization using structured interviews, review of medicine lists and measurement of biochemical parameters. Another strength was the measurement of faecal calprotectin and faecal elastase-1 to exclude previously undiagnosed inflammatory bowel disease and pancreatic exocrine insufficiency, respectively.

To conclude, we found that patients with diabetic diarrhoea had slower gastric emptying, faster colonic transit and altered gastrointestinal pH levels. Overall, our findings do not support the association between diabetic diarrhoea and autonomic dysfunction. Our results add increased knowledge to a field largely devoid of research for the last two decades. Hopefully, they provide the groundwork for further studies into the pathophysiology of diabetic diarrhoea. Our study also proves that measurement of transit times and intestinal pH levels can be a valuable guide for individualized treatment and may warrant a more central role in the evaluation of diabetic diarrhoea.

Acknowledgements

Conflict of Interest

The authors have no competing interests.

Author Contributions

Eirik Søfteland (ES) is guarantor of the article. Dag A. Sangnes (DS), Georg Dimcevski (GD) and ES designed the study. DS and ES analysed the tests. Jakub Frey (JF) and DS contributed to data entry. DS performed the statistical analysis. All authors were involved in drafting of the manuscript. All authors approved the final version of the manuscript.

Funding

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Prior Presentation

An abstract from the study was presented at the NeuroGASTRO congress in Lisbon, Portugal, September 5–7, 2019.

References

1 Selby A, Reichenbach ZW, Piech G, Friedenberg FK. Pathophysiology, differential diagnosis, and treatment of diabetic diarrhea. *Dig Dis Sci*. 2019;**64**(12):3385–93.

2 Sommers T, Mitsuhashi S, Singh P, Hirsch W, Katon J, Ballou S, et al. Prevalence of chronic constipation and chronic diarrhea in diabetic individuals in the United States. *Am J Gastroenterol*. 2019;**114**(1):135–42.

3 Ludvigsson JF, Green PH. Clinical management of coeliac disease. *J Intern Med*. 2011;**269**(6):560–71.

4 Søfteland E, Poulsen JL, Starup-Linde J, Christensen TT, Olesen SS, Singh S, et al. Pancreatic exocrine insufficiency in diabetes mellitus - prevalence and characteristics. *Eur J Intern Med*. 2019;**68**:18–22.

5 Vigren L, Tysk C, Ström M, Hjortswang H, Bohr J, Benoni C, et al. Celiac disease and other autoimmune diseases in patients with collagenous colitis. *Scand J Gastroenterol*. 2013;**48**(8):944–50.

6 Jess T, Jensen BW, Andersson M, Villumsen M, Allin KH. Inflammatory bowel diseases increase risk of type 2 diabetes in a nationwide cohort study. *Clin Gastroenterol Hepatol*. 2020;**18**(4):881–888.e1.

7 Maconi G, Furfaro F, Sciurti R, Bezzio C, Ardizzone S, de Franchis R. Glucose intolerance and diabetes mellitus in ulcerative colitis: Pathogenetic and therapeutic implications. *World J Gastroenterol*. 2014;**20**(13):3507–15.

8 Vaaler S, Bjørneklett A, Jelling I, Skrede G, Hanssen KF, Fausa O, et al. Sorbitol as a sweetener in the diet of insulin-dependent diabetes. *Acta Med Scand*. 1987;**221**(2):165–70.

9 Bytzer P, Talley NJ, Jones MP, Horowitz M. Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther*. 2001;**15**(1):137–42.

10 de Wit HM, Vervoort GM, Jansen HJ, de Galan BE, Tack CJ. Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized control. *J Intern Med*. 2016;**279**(3):283–92.

11 Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: Prevalence, assessment, pathogenesis, and management. *Diabetes Care*. 2018;**41**(3):627–37.

12 Valdovinos MA, Camilleri M, Zimmerman BR. Chronic diarrhea in diabetes mellitus: mechanisms and an approach to diagnosis and treatment. *Mayo Clin Proc*. 1993;**68**(7):691–702.

13 Samsom M, Verhagen MAMT. Intestinal Function in Diabetes Mellitus. In: Horowitz M, Samsom M, editors. *Gastrointestinal function in diabetes mellitus*. Chichester, England: Wiley; 2004. pp. 177–217.

14 Meldgaard T, Keller J, Olesen AE, Olesen SS, Krogh K, Borre M, et al. Pathophysiology and management of diabetic gastroenteropathy. *Therap Adv Gastroenterol*. 2019;**12**:1–17.

15 Malins JM, Mayne N. Diabetic diarrhea. A study of thirteen patients with jejunal biopsy. *Diabetes*. 1969;**18**(12):858–66.

16 Miller LJ. Small intestinal manifestations of diabetes mellitus. *Yale J Biol Med*. 1983;**56**(3):189–93.

17 Yarandi SS, Srinivasan S. Diabetic gastrointestinal motility disorders and the role of enteric nervous system: Current status and future directions. *Neurogastroenterol Motil*. 2014;**26**(5):611–24.

18 Dotevall G, Fagerberg SE, Langer L, Walan A. Vagal function in patients with diabetic neuropathy. *Acta Med Scand*. 1972;**191**(1-2):21–4.

19 Berge KG, Sprague RG, Bennett WA. The intestinal tract in diabetic diarrhea: a pathologic study. *Diabetes*. 1956;**5**(4):289–94.

20 Farmer AD, Wegeberg AML, Brock B, Hobson AR, Mohammed SD, Scott SM, et al. Regional gastrointestinal contractility parameters using the wireless motility capsule: inter-observer reproducibility and influence of age, gender and study country. *Aliment Pharmacol Ther*. 2018;**47**(3):391–400.

21 Wang YT, Mohammed SD, Farmer AD, Wang D, Zarate D, Hobson AR, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: Influence of age, gender, study country and testing protocol. *Aliment Pharmacol Ther*. 2015;**42**(6):761–72.

22 Eherer AJ, Fordtran JS. Fecal osmotic gap and pH in experimental diarrhea of various causes. *Gastroenterology*. 1992;**103**(2):545–51.

23 Gennari FJ, Weise WJ. Acid-base disturbances in gastrointestinal disease. *Clin J Am Soc Nephrol*. 2008;**3**(6):1861–8.

24 Farmer AD, Mohammed SD, Dukes GE, Scott SM, Hobson AR. Caecal pH is a biomarker of excessive colonic fermentation. *World J Gastroenterol*. 2014;**20**(17):5000–7.

25 Chander Roland B, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE, et al. Low ileocecal valve pressure is significantly associated with small intestinal bacterial overgrowth (SIBO). *Dig Dis Sci*. 2014;**59**(6):1269–77.

26 Sangnes DA, Søfteland E, Bekkelund M, Frey J, Biermann M, Gilja OH, et al. Wireless motility capsule compared with scintigraphy in the assessment of diabetic gastroparesis. *Neurogastroenterol Motil*. 2020;**32**(4):e13771.

27 Søfteland E, Brock C, Frøkjær JB, Brøgger J, Madácsy L, Gilja OH, et al. Association between visceral, cardiac and sensorimotor polyneuropathies in diabetes mellitus. *J Diabetes Complications*. 2014;**28**(3):370–77.

28 Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care*. 2003;**26**(5):1553–79.

29 Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. *Scand J Gastroenterol*. 1995;**30**(11):1046–52.

30 Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: L. Erlbaum Associates; 1988.

31 Dooley CP, el Newihi HM, Zeidler A, Valenzuela JE. Abnormalities of the migrating motor complex in diabetics with autonomic neuropathy and diarrhea. *Scand J Gastroenterol*. 1988;**23**(2):217–23.

32 Rosa-e-Silva L, Troncon LEA, Oliveira RB, Foss MC, Braga FJHN, Gallo L. Rapid distal small bowel transit associated with sympathetic denervation in type I diabetes mellitus. *Gut*. 1996;**39**(5):748–56.

33 Rana S V, Malik A, Bhadada SK, Sachdeva N, Morya RK, Sharma G. Malabsorption, orocecal transit time and small intestinal bacterial overgrowth in Type 2 diabetic patients: a connection. *Indian J Clin Biochem*. 2017;**32**(1):84–9.

34 Scarpello JH, Hague RV, Cullen DR, Sladen GE. The 14C-glycocholate test in diabetic diarrhoea. *Br Med J*. 1976;**2**(6037):673–75.

35 Meyer C, O'Neal DN, Connell W, Alford F, Ward G, Jenkins AJ. Octreotide treatment of severe diabetic diarrhoea. *Intern Med J*. 2003;**33**(12):617–18.

36 Wegeberg AML, Brock C, Ejskjaer N, Karmisholt JS, Jakobsen P-K, Drewes AM, et al. Gastrointestinal symptoms and cardiac vagal tone in type 1 diabetes correlates with gut transit times and motility index. *Neurogastroenterol Motil*. 2021;**33**(1):e13885.

37 Duchen LW, Anjorin A, Watkins PJ, Mackay JD. Pathology of autonomic neuropathy in diabetes mellitus. *Ann Intern Med*. 1980;**92**(2 II):301–3.

38 Whalen GE, Soergel KH, Geenen JE. Diabetic diarrhea. A clinical and pathophysiological study. *Gastroenterology*. 1969;**56**(6):1021–32.

39 Frøkjaer JB, Andersen SD, Ejskjaer N, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, et al. Gut sensations in diabetic autonomic neuropathy. *Pain*. 2007;**131**(3):320–9.

40 Søfteland E, Brock C, Frøkjær JB, Simrén M, Drewes AM, Dimcevski G. Rectal sensitivity in diabetes patients with symptoms of gastroparesis. *J Diabetes Res*. 2014;**2014**:1–8.

41 Kumar A, Attaluri A, Hashmi S, Schulze KS, Rao SSC. Visceral hypersensitivity and impaired accommodation in refractory diabetic gastroparesis. *Neurogastroenterol Motil*. 2008;**20**(6):635–42.

42 Clouse RE, Lustman PJ. Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy. *Am J Gastroenterol*. 1989;**84**(8):868–82.

43 Punkkinen J, Färkkilä M, Mätzke S, Korppi-Tommola T, Sane T, Piirilä P, et al. Upper abdominal symptoms in patients with Type 1 diabetes: unrelated to impairment in gastric emptying caused by autonomic neuropathy. *Diabet Med*. 2008;**25**(5):570–7.

44 Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. 2017;**5**:258.

45 Saghazadeh-Dezfuli M, Fanaei H, Gharib-Naseri MK, Nasri S, Mard SA. Antidiarrheal effect of sodium hydrosulfide in diabetic rats: In vitro and in vivo studies. *Neurogastroenterol Motil*. 2018;**30**(10):e13273.

46 Kårhus ML, Brønden A, Røder ME, Leotta S, Sonne DP, Knop FK. Remission of bile acid malabsorption symptoms following

treatment with the glucagon-like peptide 1 receptor agonist liraglutide. *Gastroenterology*. 2019;**157**(2):569–71.

47 Vijayvargiya P, Camilleri M. Update on bile acid malabsorption: finally ready for prime time? *Curr Gastroenterol Rep*. 2018;**20**(3):10.

48 Hammer HF, Hammer J. Diarrhea Caused By Carbohydrate Malabsorption. *Gastroenterol Clin North Am*. 2012;**41**(3):611–27.

49 Farmer AD, Pedersen AG, Brock B, Jakobsen PE, Karmisholt J, Mohammed SD, et al. Type 1 diabetic patients with peripheral neuropathy have pan-enteric prolongation of gastrointestinal transit times and an altered caecal pH profile. *Diabetologia*. 2017;**60**(4):709–18.

50 Wegeberg AML, Brock C, Brock B, Farmer AD, Hobson AR, Semler JR, et al. Regional gastrointestinal pH profile is altered in patients with type 1 diabetes and peripheral neuropathy. *Neurogastroenterol Motil*. 2018;**30**(11):1–10.

51 Farmer AD, Ruffle JK, Hobson AR. Linaclotide increases cecal pH, accelerates colonic transit, and increases colonic motility in irritable bowel syndrome with constipation. *Neurogastroenterol Motil*. 2019;**31**(2).

52 Nugent SG, Kumar D, Rampton DS, Evans DF. Intestinal luminal pH in inflammatory bowel disease: Possible determinants and implications for therapy with aminosalicylates and other drugs. *Gut*. 2001;**48**(4):571–7.

53 Tottey W, Feria-Gervasio D, Gaci N, Laillet B, Pujos E, Martin J-F, et al. Colonic transit time is a driven force of the gut microbiota composition and metabolism: in vitro evidence. *J Neurogastroenterol Motil*. 2017;**23**(1):124–34.

54 von Volkmann HL, Brønstad I, Gilja OH, Tronstad RR, Sangnes DA, Nortvedt R, et al. Prolonged intestinal transit and diarrhea in patients with an activating GUCY2C mutation. *PLoS One*. 2017;**12**(9):e0185496.

55 Fallingborg J, Pedersen P, Jacobsen BA. Small intestinal transit time and intraluminal pH in ileocecal resected patients with Crohn's disease. *Dig Dis Sci*. 1998;**43**(4):702–5.

56 Rouphael C, Arora Z, Thota PN, Lopez R, Santisi J, Funk C, et al. Role of wireless motility capsule in the assessment and management of gastrointestinal dysmotility in patients with diabetes mellitus. *Neurogastroenterol Motil*. 2017;**29**(9): 1–7.

57 Murao S, Hosokawa H. Serotonin 5-HT3 receptor antagonist for treatment of severe diabetic diarrhea. *Diabetes Care*. 2010;**33**(3):e38.

58 Fragkos KC, Zárate-Lopez N, Frangos CC. What about clonidine for diarrhoea? A systematic review and meta-analysis of its effect in humans. *Therap Adv Gastroenterol*. 2016;**9**(3):282–301.

59 Holzer P. Acid-sensing ion channels in gastrointestinal function. *Neuropharmacology*. 2015;**94**:72–9.

60 Zarate N, Newell M, Yazaki E, Newell M, Yazaki E, Williams NS, et al. Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique. *Am J Physiol Liver Physiol*. 2010;**299**(6):G1276–86.

61 Coleski R, Wilding GE, Semler JR, Hasler WL. Blunting of colon contractions in diabetics with gastroparesis quantified by wireless motility capsule methods. *PLoS One*. 2015;**10**(10):1–15.

62 Damholt MB, Arlien-Soeborg P, Hilsted L, Hilsted J. Is pancreatic polypeptide response to food ingestion a reliable index of vagal function in type 1 diabetes? *Scand J Clin Lab Invest*. 2006;**66**(4):279–86.

63 Buysschaert M, Donckier J, Dive A, Ketelslegers J-M, Lambert AE. Gastric acid and pancreatic polypeptide responses to sham feeding are impaired in diabetic subjects with autonomic neuropathy. *Diabetes*. 1985;**34**(11):1181–5.

64 EFLM Biological variation Database. (n.d). https://biologicalvariation.eu/. Accessed March 31, 2021.

Correspondence

Dag A. Sangnes, Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway.
Email: dag.andre.sangnes@helse-bergen.no; dsangnes@gmail.com

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting information ■